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SYNTHESIS OF NATURAL LIGNAN ARYLNAPHTHALENE LACTONES, DAURINOL AND RETROCHINENSIN

PAUL T. ANASTAS and ROBERT STEVENSON*

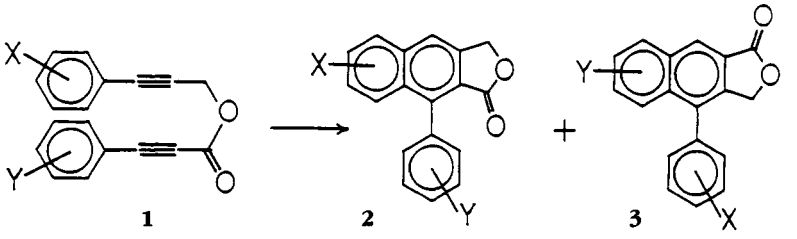
Department of Chemistry, Brandeis University, Waltham, Massachusetts 02254

ABSTRACT.—Two natural arylnaphthalene lignan lactones, daurinol [**4**] and retrochinensin [**5**], have been synthesized by a short reaction pathway from isovanillin. By heating in xylenes, the ester 3-benzyloxy-4-methoxyphenylpropargyl 3,4-methylenedioxyphenylpropiolate [**14**] yielded daurinol benzyl ether [**15**] and 1-(3′-benzyloxy-4′-methoxyphenyl)-2-hydroxymethyl-6,7-methylenedioxy-3-naphthoic acid lactone [**17**]. Debenzylation of **15** gave daurinol [**4**], and debenzylation of **17** followed by methylation yielded retrochinensin [**5**].

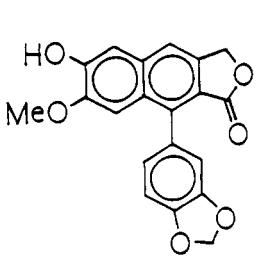
About forty natural arylnaphthalenes, the majority of which are lactones, are now known and represent a significant subclass of lignans. A review of the biological activities of lignans (1) emphasizes an impressive variety, and among the arylnaphthalene group, antitumor (2), antidepressant (3), and antiviral action (4) have been displayed. It has recently been shown (5) that arylpropargyl arylpropiolates (general structure **1**) upon heating in xylene undergo cyclization in excellent yield and with insignificant regioselectivity to yield the corresponding arylnaphthalene lactones **2** and **3** (Scheme 1). We now report an unequivocal synthesis of the natural lignans daurinol [**4**] and retrochinensin [**5**] using this key step.

Daurinol was first isolated as a constituent, $C_{20}H_{14}O_6$, of *Haplophyllum dauricum* (L.) G. Don (Rutaceae) (6) and more recently from two natural glycerides obtained from *Haplophyllum buxbaumii* (7). Since CH_2N_2 methylation of daurinol yielded justicidin B [**6**], it must have either structure **7** or **4** (6). The structure assignment of the biogenetically less likely structure **4** came from extensive proton double resonance (8) and ^{13}C nmr (9) studies. Whereas the vanillyl (3-OMe-4-OH) structural moiety is of common occurrence among lignans of all classes, the isovanillyl (3-OH-4-OMe) fragment is extremely rare and in some cases based on equivocal evidence. Since the proposed constitution of daurinol incorporates this latter feature, we have undertaken a synthesis in the interest of structure verification and for biological screening of the natural product.

Benzylation of isovanillin [**8**] by a modified procedure (10) gave the benzyl ether **9**, which on treatment with triethyl phosphonoiodoacetate (Wadsworth-Emmons procedure for propiolate ester synthesis) followed by base hydrolysis, yielded 3-benzyloxy-4-methoxyphenylpropiolic acid [**10**] in 59% yield. The required arylpropargyl alcohol **12** was then conveniently obtained by diisobutylaluminum hydride reduction of the derived ethyl ester **11**. After heating the alcohol **12** with 3,4-methylenedioxy-



SCHEME 1



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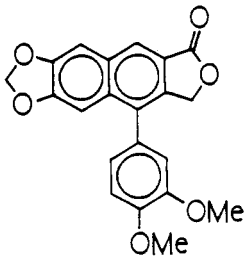

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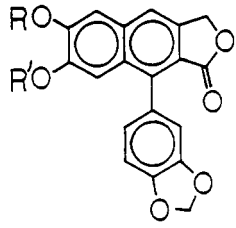
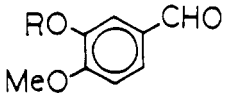


6 R=R′=Me
7 R=Me, R′=H

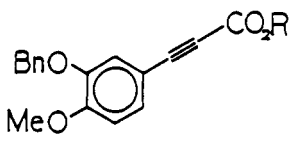
phenylpropiolyl chloride [**13**] in pyridine, examination (^{1}H nmr and tlc) of the crude product indicated formation of the desired ester **14** together with minor quantities of the lactones **15** and **17**. Without separation of this product mixture, cyclization to form the lactones quantitatively was completed by heating under reflux with xylene. Separation of the isomers **15** and **17**, produced as expected in essentially equimolar ratio, was effected by flash chromatography. These products were readily distinguished by their ^{1}H-nmr spectra, notably by the chemical shifts of the lactone methylene protons and the H-4 benzenoid protons.

The synthesis of daurinol [**4**] was completed by debenzylation of 1-(3′,4′-methylenedioxyphenyl)-3-hydroxymethyl-6-benzyloxy-7-methoxy-2-naphthoic acid lactone [**15**]. A recently described catalytic transfer hydrogenation procedure (11), using palladium on carbon with ammonium formate as the hydrogen donor, cleanly yielded daurinol [**4**] with mp and spectrometric data (^{1}H nmr, ^{13}C nmr) in excellent agreement with those reported for both the phenol and the acetate derivative **16**.

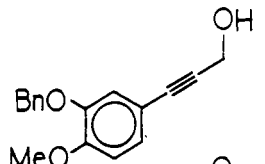
Similar debenzylation of the isomeric lactone, 1-(3′-benzyloxy-4′-methoxyphenyl)-2-hydroxymethyl-6,7-methylene-



8 R=H
9 R=Bn



10 R=H
11 R=C_2H_5



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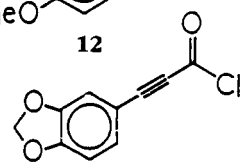

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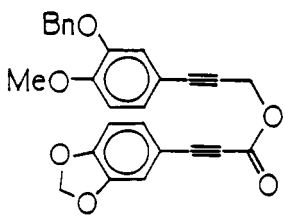
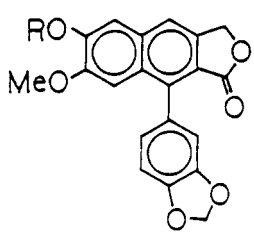
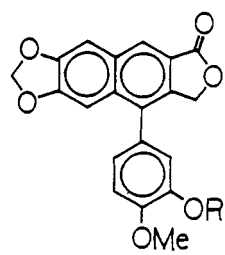


14



15 R=Bn
16 R=Ac



17 R=Bn
18 R=H

dioxy-3-naphthoic acid lactone [**17**] gave the phenol **18** which on methylation gave retrochinensin [**5**], which was first isolated naturally as a constituent of an antidepressant extract from *Justicia prostata* (Acanthaceae) in 1979 (3) but which had in fact been synthesized previously (12).

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—^{1}H-nmr and ^{13}C-nmr spectra were determined with TMS as internal standard, using Varian EM390 and XL300 spectrometers. Tlc analyses were carried out on Kodak Chromagram Si gel sheets (20 × 20 cm) with product detection by uv fluorescence or I_2 vapor absorption. Cc was conducted on Si gel (Kieselgel 40, 70–239 mesh, EM Science).

3-BENZYLOXY-4-METHOXYBENZALDEHYDE [**9**].—Anhydrous K_2CO_3 (74.0 g) and benzyl chloride (66.0 g) were added to a stirred solution of 4-methoxy-3-hydroxybenzaldehyde [**8**] (40.0 g) in dry Me_2CO, and the mixture was heated under reflux for 20 h. The cooled mixture was diluted with H_2O (500 ml) and extracted with $CHCl_3$ (3 × 150 ml). Evaporation of the washed and dried organic extract yielded a yellow gum which was dissolved in EtOH (200 ml) and stirred with a saturated solution of aqueous $NaHSO_3$ (300 ml). The resulting precipitate was collected, stirred overnight in dilute H_2SO_4 solution, and extracted with Et_2O. Evaporation of the washed and dried extract gave a residue which, on crystallization from EtOH, gave the benzyl ether **9** as plates (71% yield): mp 60–61.5° [lit. (10) mp 62–63°]; ^{1}H nmr ($CDCl_3$) δ 3.96 (s, OMe), 5.19 (s, CH_2), 6.99 (d, J = 9 Hz, H-5′), 7.26–7.48 (m, seven ArH).

3-BENZYLOXY-4-METHOXYPHENYLPROPIOLIC ACID [**10**].—A solution of triethyl phosphonoacetate (18.50 g) in dry THF (150 ml) was added dropwise over 30 min to a stirred suspension of NaH (3.25 g, 60% mineral oil suspension) in dry THF with cooling below 10°. When H_2 evolution had ceased, a solution of I_2 (20.65 g) in THF (200 ml) was added over 30 min, and the mixture was stirred for 2 h. NaH (6.50 g, 60%) was then added in one batch, and after gas evolution had ceased a solution of isovanillin benzyl ether [**9**] (20.00 g) in dry THF (150 ml) was added dropwise over 30 min. The mixture was then warmed at 40° for 4 h, cooled, poured into ice-H_2O (700 ml), and extracted with Et_2O (3 × 250 ml). Evaporation of the washed and dried extract yielded a brown viscous oil, the ms of which indicated the presence of the desired propiolate ester [**11**] and intermediate iodo-cinnamate ester. A portion (0.5 g) of this mixture ws stirred overnight at room temperature with a solution of KOH (1.67 g) in EtOH (10 ml), diluted with H_2O (25 ml), and acidified with concentrated HCl. The resultant precipitate was crystallized once from EtOH to give the acetylenic acid **10** as a white solid: mp 180–182° (59% yield); ^{1}H nmr [$(CD_3)_2CO$] 3.82 (s, OMe), 5.07 (s, OCH_2Ph), 6.90 (d, J = 9 Hz, H-5), 6.95 (d, J = 2 Hz, H-2), 7.35–7.45 (m, six ArH); eims *m/z* 282.0906 ($C_{17}H_{14}O_4$ requires 282.0892).

ETHYL 3-BENZYLOXY-4-METHOXYPHENYLPROPIOLATE [**11**].—Concentrated HCl (2.0 ml) was added to a solution of the acid **10** (10.0 g) in EtOH. The mixture was heated under reflux overnight and the solvent removed under reduced pressure. The residue was dissolved in Et_2O and washed successively with H_2O, saturated aqueous $NaHCO_3$ solution, and H_2O. Evaporation of the dried organic extract gave a brown solid (8.07 g) which was dissolved in $CHCl_3$ and filtered through Si gel. Crystallization of the eluate from $CHCl_3$ gave ethyl 3-benzyloxy-4-methoxyphenylpropiolate [**11**] (6.47 g): mp 82–83°; ^{1}H nmr ($CDCl_3$) δ 1.35 (t, J = 9 Hz, Me), 3.91 (s, OMe), 4.28 (q, J = 9 Hz, OCH_2CH_3), 5.12 (s, OCH_2Ph), 6.86 (d, J = 9 Hz, H-5), 7.11 (d, J = 2 Hz, H-2), 7.25 (dd, J = 9, 2 Hz, H-6), 7.30–7.44 (m, five ArH). Found C 73.3, H 5.85; $C_{19}H_{18}O_4$ requires C 73.5, H 5.85%.

3-BENZYLOXY-4-METHOXYPHENYLPROPARGYL ALCOHOL [**12**].—Di-isobutylaluminum hydride (23.50 ml of a 1.0 M solution in hexane) was added by syringe to a solution of ethyl 3-benzyloxy-4-methoxyphenylpropiolate [**11**] (3.59 g) in THF (30 ml) at −78° under N_2. After the mixture had warmed to room temperature, addition of saturated NH_4Cl solution (3.0 ml) produced a colloidal solution that was dispersed by addition of 10% aqueous HCl (6.0 ml). Et_2O (50 ml) was added, and the organic layer was washed with 10% aqueous HCl (2 × 50 ml), brine (2 × 50 ml), and H_2O (50 ml). Evaporation of the dried extract and crystallization of the residue from $CHCl_3$ gave 3-benzyloxy-4-methoxyphenylpropargyl alcohol [**12**] (3.0 g, 92% yield) as a white solid: mp 88–89°; ^{1}H nmr ($CDCl_3$) δ 3.86 (s, OMe), 4.40 (s, CH_2OH), 5.07 (s, CH_2Ph), 6.81 (dd, J = 8, 2 Hz, H-5), 6.98 (d, J = 2 Hz, H-2), 7.03 (d, J = 8 Hz), 7.33–7.44 (m, five ArH); eims *m/z* 268.1079 ($C_{17}H_{16}O_3$ requires 268.1099).

FORMATION AND INTRAMOLECULAR CYCLIZATION OF 3-BENZYLOXY-4-METHOXYPHENYLPROPARGYL 3,4-METHYLENEDIOXYPHENYLPROPIOLATE [**14**].—3,4-Methylenedioxyphenylpropiolic acid (2.13 g) was added to freshly distilled thionyl chloride at room temperature with stirring until solution was complete (ca. 3 h). Excess reagent was removed by repeated addition of

C_6H_6 and evaporation under reduced pressure. The residual acid chloride **13** was dissolved in C_6H_6 (100 ml) and added to a solution of 3-benzyloxy-4-methoxyphenylpropargyl alcohol **[12]** (3.00 g) in pyridine (1.50 ml). The mixture was heated under reflux (N_2 atmosphere) for 5 h and worked up in the usual way. Tlc (Si gel, $CHCl_3$) examination of the product showed the absence of starting alcohol **12** and presence of desired ester **14** (front running) and cyclized lactone products **15** and **17** (R_f 0.5, fluorescent streak). This crude reaction mixture (4.81 g) was dissolved in xylenes (50 ml) and heated under reflux for 5 h, and the solvent was then removed under reduced pressure to yield a dark brown viscous oil (4.80 g). A portion (500 mg) was subjected to flash chromatography on Si gel with petroleum ether-EtOAc (4:1) under a positive pressure of N_2, and 20-ml aliquots were collected and assayed by tlc. Fractions 10–35 yielded a light yellow oil which crystallized from MeOH to give 1-(3′-benzyloxy-4′-methoxyphenyl)-2-hydroxymethyl-6,7-methylenedioxy-3-naphthoic acid lactone **[17]** as a white solid (151 mg): mp 220–223°; eims *m/z* 440.1273 ($C_{27}H_{20}O_6$ requires 440.1260); ^{1}H nmr ($CDCl_3$) δ 3.99 (s, OMe), 4.78 and 5.00 (each d, J = 15 Hz, $PhCH_2O$- or $ArCH_2O$-), 5.16 and 5.24 (each d, J = 13 Hz, $ArCH_2O$- or $PhCH_2O$-), 6.09 (s, OCH_2O), 6.79 (d, J = 2 Hz, H-2′), 6.88 (dd, J = 8, 2 Hz, H-6′), 7.03 (s, H-8), 7.04 (d, J = 8 Hz, H-5′), 7.25–7.38 (m, six ArH), 8.22 (s, H-4).

Fractions 36–60 gave an oil (173 mg) shown by tlc to be a mixture.

Fractions 61–120 on solvent evaporation and recrystallization from MeOH gave 1-(3′,4′-methylenedioxyphenyl)-3-hydroxymethyl-6-benzyloxy-7-methoxy-2-naphthoic acid lactone (daurinol benzyl ether) **[15]** as a white solid (152 mg): mp 233–234°; eims *m/z* 440.1264 ($C_{27}H_{20}O_6$ requires 440.1260); ^{1}H nmr ($CDCl_3$) δ 3.81 (s, OMe), 5.32 (s, $ArCH_2O$- or $PhCH_2O$-), 5.35 (s, $PhCH_2O$- or $ArCH_2O$-), 6.06 and 6.10 (each d, J = 1.5 Hz, OCH_2O), 6.81–6.85 (m, H-2′ and 6′), 6.96 (d, J = 8 Hz, H-5′), 7.13 (s, H-8), 7.21 (s, H-5), 7.26–7.50 (m, five ArH), 7.63 (s, H-4).

1-(3′,4′-METHYLENEDIOXYPHENYL)-3-HYDROXYMETHYL-6-HYDROXY-7-METHOXY-2-NAPHTHOIC ACID LACTONE (DAURINOL) **[4]**.—Ammonium formate (30 mg) and 10% Pd/C (500 mg) were added to a stirred solution of daurinol benzyl ether **[15]** (53 mg) in Me_2CO (30 ml) which was then heated under reflux for 45 min, cooled, filtered, and evaporated under reduced pressure. The residue was dissolved in $CHCl_3$, washed with H_2O (25 h), and extracted with 5% NaOH solution (2 × 15 ml). The basic layer was acidified with concentrated HCl, extracted with Et_2O, and worked up in the usual way. One crystallization of the product from MeOH gave daurinol **[4]** as a white solid (13 mg): mp 250–253° (lit. (6) mp 256–257°]; ^{1}H nmr ($CDCl_3$) δ 3.87 (s, OMe), 5.38 (s, $ArCH_2O$), 6.06 and 6.11 (each d, J = 1.5 Hz, OCH_2O), 6.82–6.86 (m, H-2′ and -6′), 6.97 (d, J = 7 Hz, H-5′), 7.11 (s, H-8), 7.34 (s, H-5), 7.69 (s, H-4); ^{13}C nmr ($CDCl_3$) δ in good agreement with that reported (9) in DMSO.

DAURINOL ACETATE **[16]**.—A solution of daurinol **[4]** (5 mg) in pyridine (5 drops) and Ac_2O (5 drops) was heated on a steam bath for 1 h. Removal of solvents under reduced pressure gave a residue of the acetate **16**: ^{1}H nmr ($CDCl_3$) δ 2.39 (s, OAc), 3.77 (s, OMe), 5.41 (s, $ArCH_2O$), 6.06 and 6.11 (each d, J = 1.5 Hz), 6.98 (d, J = 8 Hz, H-5′), 6.82–6.86 (m, H-2′ and -6′), 7.21 (s, H-8), 7.60 (s, H-5), 7.77 (s, H-4).

RETROCHINENSIN **[5]**.—Ammonium formate (200 mg) and 10% Pd/C (1.0 g) were added to a stirred solution of the lactone benzyl ether **17** (100 mg) in Me_2CO (25 ml), and the mixture was heated under reflux for 1.5 h. Filtration and evaporation gave 1-(3′-hydroxy-4′-methoxyphenyl)-2-hydroxymethyl-6,7-methylenedioxy-3-naphthoic acid lactone **[18]** as a clear yellow oil (65 mg, 82% yield): ^{1}H nmr ($CDCl_3$) δ 3.84 (s, OMe), 5.07 (br s, $ArCH_2O$), 5.95 (s, OCH_2O), 6.67 (dd, J = 8, 2 Hz, H-6′), 6.77 (d, J = 2 Hz, H-2′), 6.87 (d, J = 8 Hz, H-5′), 7.00 (s, H-8), 7.16 (s, H-5), 8.11 (s, H-4). To a stirred solution of this phenolic lactone **18** (60 mg) in Me_2CO (30 ml), Me_2SO_4 (0.5 ml) and K_2CO_3 (10 g) were added and the mixture heated under reflux for 30 min, then worked up in the usual way by aqueous dilution and $CHCl_3$ extraction. Evaporation of the washed and dried extract gave 1-(3′,4′-dimethoxylphenyl)-3-hydroxymethyl-6,7-methylenedioxy-2-naphthoic acid lactone (retrochinensin) **[5]**, which crystallized from MeOH as needles: mp 232–234° [lit. (3) mp 234°]; ^{1}H nmr ($CDCl_3$) δ 3.89 (s, OMe), 3.99 (s, OMe), 5.18 and 5.24 (each d, J = 10 Hz, $ArCH_2O$), 6.10 (br s, OCH_2O), 6.84 (d, J = 2 Hz, H-2′), 6.90 (dd, J = 8, 2 Hz, H-6′), 7.04 (d, J = 8 Hz, H-5′), 7.10 (s, H-8), 7.32 (s, H-5), 8.28 (s, H-4).

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LITERATURE CITED

1. W.D. MacRae and G.H.N. Towers, *Phytochemistry*, **23**, 1207 (1984).
2. A.G. Gonzales, V. Darias, and G. Alonso, *Planta Med.*, **36**, 200 (1979).

3. S. Ghosal, S. Banerjee and A.W. Frahm, *Chem. Ind. (London)*, 854 (1979).
4. W.D. MacRae, J.B. Hudson, and G.H.N. Towers, *Planta Med.*, **55**, 531 (1989).
5. R. Stevenson and J.V. Weber, *J. Nat. Prod.*, **52**, 367 (1989).
6. D. Batsuren, E.Kh. Batirov, V.M. Malikov, V.N. Zemlyanskii, and M.R. Yagudaev, *Chem. Nat. Compd., Engl. Transl.*, **17**, 223 (1981).
7. Y. Al-Abed, S. Sabri, M.A. Zarga, Z. Shah, and Atta-ur-Rahman, *Phytochemistry*, **29**, 2659 (1990).
8. D. Batsuren, M.R. Yagudaev, E.Kh. Batirov, and V.M. Malikov, *Chem. Nat. Compd. (Engl. Transl.)*, **19**, 17 (1983).
9. N.D. Abdullaev, M.R. Yagudaev, E.Kh. Batirov, and V.M. Malikov, *Chem. Nat. Compd. (Engl. Transl.)*, **23**, 63 (1987).
10. A. Lovecy, R. Robinson, and S. Sugasawa, *J. Chem. Soc.*, 877 (1930).
11. T. Bieg and W. Szeja, *Synthesis*, 76 (1985).
12. K. Munakata, S. Marumo, K. Ohta, and Y.L. Chen, *Tetrahedron Lett.*, 3821 (1967).

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